30.(Amended) A therapeutic composition comprising an IgSF domain or fragment, or a fusion protein comprising an IgSF domain or fragment, according to:

i. claim 28

ii. claim 35; or

iii. claim 36.

31.(Amended) A method for deriving a DNA sequence according to [any of] claim[s] 1 [to 25] which comprises the following steps:

i) analyzing the interface region of a parent IgSF domain for hydrophobic residues which are solvent-exposed,

ii) identifying one or more of the hydrophobic residues to be substituted by more hydrophilic residues, or one or more positions where hydrophilic residues or amino acid stretches enhancing the overall hydrophilicity of the interface region can be inserted into said interface region, or one or more positions where hydrophobic residues or amino acid stretches enhancing the overall hydrophobicity of the interface region can be deleted from said interface region, or any combination of said substitutions, said insertions, and said deletions to give one or more mutants of said parent IgSF domain.

32. (Amended) A method for making an IgSF domain or fragment, or a fusion protein comprising an IgSF domain or

fragment, according to claim 28 which comprises the following steps:

i) deriving a DNA sequence according to claim 31[,];

ii) preparing DNA encoding said mutant or mutants, said DNA being prepared either separately or as a mixture[,];

iii) introducing said DNA or DNA mixture in a vector system suitable for expression of said mutant or mutants, said vector system optionally comprising one or more additional DNA sequences suitable for expression of additional IgSF domains or fragments, or one or more DNA sequences suitable for expression of a fusion protein comprising said mutant or mutants, or any combination of said additional DNA sequences[.];

iv) introducing said vector system into suitable host cells and expressing said mutant or mixture of mutants, or expressing said mutants or mixture of mutants in combination with the expression products of said additional DNA sequences[,];

v) identifying and characterizing one or more mutants, alone or in said combination, which are obtained in higher yield in soluble form[,]; and

vi) if necessary, repeating steps ii) to vi) to increase the hydrophilicity of said identified mutant or mutants, alone or in said combination, further.

Delete page 23, line 1 through page 25, line 10 and substitute therefor:

-- Description of Figures

Figure 1 provides a space filling representation of the Fv fragment of the antibody 4-4-20.

Figure 2 presents the variable/constant domain interface residues for V_L (2a) and V_H (2b). For 30 non-redundant Fab fragments taken from the Brookhaven Databank, the solvent accessible surface of the amino acid side chains was calculated in the context of an Fv and of an Fab fragment. The plot shows the relative reduction in accessible surface upon contact with the constant domains (overlay plot for all 30 Fv fragments). In the sequence alignment, residues contributing to the v/c interface are highlighted. The symbols indicate the relative reduction of solvent accessible surface upon removing the constant domains (symbols: no symbol < 1%; l < 20%; n < 40%; s < 60%; t < 80%, and u ³ 80%). Circles indicate those positions which are further analyzed (see Table 1).

Figure 3 presents Western blots showing the insoluble (i) and soluble (s) fractions of cell extracts, prepared as described in Material and Methods, expressing the scFv fragments of the antibody 4-4-20. The amino acids substituted in the various mutants are given in Table 2.

Figure 4 presents a Scatchard plot of the fluorescence titration of fluorescein (20 nM) with antibody (4 to 800 nM), measured at 510 nm. The value r was obtained from $(F-F_o)/(F¥-F_o)$,

where F is the measured fluorescein fluorescence at a given antibody concentration, F_o is the fluorescence in the absence of antibody and F_∞ when antibody is present in large excess. Note that r gives the saturation of fluorescein by antibody. (a) Titration of wt scFv, (b) titration of Flu4 (V84D).

Figure 5 presents an overlay plot of the urea denaturation curves ((X) wt scFv, (o) Flu4).

Figure 6 presents the thermal denaturation time courses at 40 and 44°C for wt and Flu4 scFv fragment ((a) wt scFv at 40°C, (b) Flu4 at 40°C, (c) Flu4 at 44°C, (d) wt scFv at 44°C).

Table 1 describes the sequence variability of residues contributing to the v/c interface. Residue statistics are based on the variable domain sequences in the Kabat database (March 1996). Sequences which were <90% complete were excluded from the analysis. Number of sequences analyzed: human VL kappa: 404 of 881, murine VL kappa: 1061 of 2239, human VL lambda: 223 of 409, murine VL lambda: 71 of 206, human VH: 663 of 1756, murine VH: 1294 of 3849. Position refers to the sequence position according to Kabat et al. 1991, %exp. (Fab) to the relative side chain accessibility in an Fab fragment as calculated by the program NACCESS (NACCESS v2.0 by Simon Hubbard (http://www.biochem.ucl.ac.uk/~roman/naccess/naccess.html), %exp. (ind.) to the relative side chain accessibility in the isolated VL or VH domain, %buried to the relative difference in side chain accessibility between Fv and Fab fragment. Consensus refers to the

sequence consensus, and Distribution to the distribution of residue types.

Table 2 describes mutations introduced in the scFv fragment of the antibody 4-4-20. Each line represents a different protein carrying the mutations indicated. The residues are numbered according to Kabat et al. (1991).

Table 3 describes K_D values of the different scFv mutants determined in fluorescence titration. The K_D values are given in nM, the error was calculated from the Scatchard analysis (Fig. 4). # determined by Miklasz et al. (1995).

The following examples illustrate the invention. --

IN THE CLAIMS

On page 34, line 1, delete "Claims" and substitute therefor -- We claim: --

Add claims 35 and 36.

Kindly amend the claims as follows:

1. (Amended) A DNA sequence [which encodes an] capable of encoding a modified immunoglobulin superfamily (IgSF) domain or fragment, wherein said modified IGSF [which] differs from a parent IgSF domain or fragment in that [the] a region which comprised or would comprise an [the] interface with a second domain adjoined to said parent IgSF domain or fragment within the chain of a larger IgSF fragment or protein is made more hydrophilic by modification.

2. (Amended) The DNA sequence according to claim 1 in which said modification is substitution of one or more amino acids